Effects of prednisone on blood lactate values in healthy dogs

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Introduction

With the advent of handheld lactate meters, the measurement of blood lactate is becoming common practice in the veterinary profession. There are two stereoisomers of lactate; an L form and a D form. The L form is the predominant form produced by mammalian cells and the sterioisomer that most laboratory and hand held lactate meters measure (Pang, Lagutchuck). As such it is the more clinically relevant form of lactate measured in veterinary medicine and the form referred to throughout the rest of this paper. Extensive reviews on both the L and D sterioisomers are available in the veterinary and human literature (Pang, Lagutchik, Ewaschuk).

In the majority of cases, blood lactate is measured to help identify and treat the presence of type A hyperlactatemia due to states of hypoperfusion. However, other causes of hyperlactatemia exist, including type B hyperlactatemia, which is not associated with states of hypoperfusion. To the authors' knowledge type B hyperlactatemia has not been extensively studied in the veterinary profession. (Pang). Although the lactate molecules derived from type A and type B conditions are identical and can not be differentiated based on biochemical analysis it is

important to identify the origin of hyperlactatemia as clinical management of the two conditions may be quite different. While all causes of hyperlactatemia require identification and correction of the underlying cause, treatment of type A hyperlactatemia usually requires aggressive fluid therapy and the administration of hemoglobin carrying/or transport solutions whereas treatment of type B hyperlactatemia often does not.

As glucocorticoids have known affects on carbohydrate and lactate metabolism, it is conceivable that therapeutically appropriate doses of glucocorticoids could result in clinically relevant type B hyperlactatemia (Heneman, MaMahon). In some instances patients receiving glucocorticoids may also have an underlying disease state associated with hypoperfusion and type A hyperlactatemia. Immune mediated haemolytic anemia (IMHA) for example, is a common disease of dogs requiring high dose glucocorticoid therapy that may also be associated with hypoperfusion as a result of red blood cell destruction, vomiting and decreased fluid intake (ref?). In cases of IMHA, blood lactate measurement has been used to help guide decisions regarding the need for blood products and aggressive fluid therapy (ref?). Determining if glucocorticoids could result in hyperlactatemia, irrespective of red blood cell counts and hypoperfused states, is important to help guide appropriate decisions regarding blood transfusion and fluid therapy. The aim of this study was to determine if oral prednisolone could result in an increase in blood lactate levels (Type B hyperlactataemia) in healthy dogs.

Materials and Methods

Twelve, neutered, healthy adult beagles (median 11.7 kg, range 9.3-15 kg) were divided into 2 equal groups of 6 dogs (3 of each sex per group). All dogs had physical

examinations, biochemistry profiles (Synchron CX ® 5, Beckman Coulter, Fullerton, California, USA) and complete blood cell counts (Cell-Dyne ® 3500, Abbott Illinois, USA) performed prior to starting the study. One group of dogs served as a control group and received placebo pill pockets (manufacturer's details?) once daily for 2 weeks. The other group received 2 treatments: LOW, 1 mg kg^{-1} oral prednisone once daily for 2 weeks; HIGH, 4 mg kg^{-1} of oral prednisone once daily for 2 weeks. All prednisone treatments were administered within pill pockets. There was a washout period of 6 weeks between treatments. All dogs had physical examinations performed at the start of each treatment period, once daily during the two weeks of placebo or prednisone administration, and once weekly during the washout period. All physical examinations were performed by an experienced veterinarian (LR). Animals were cared for according to the principles outlined by the Canadian Council on Animal Care Guide to the Care and Use of Experimental Animals. All procedures were approved by the Ethics Committee for the Utilisation of Animals for the University of Montreal. The dogs were housed under identical conditions in an environmentally controlled room. They were fed a commercial dry diet and had free access to water. Blood was collected directly into a 3 mL lithium heparinised tube (Monoject, Tyco Healthcare Group LP, Mansfield, Massachusetts, USA) using jugular venipuncture and a 21g butterfly needle attached to a vacutainer system (Vacutainer ® Brand Blood Collection Set, Becton Dickinson and Company, Franklin Lakes, New Jersey, USA). In cases of a technical delay in collecting blood or slow (> 15secs) filling of the collection tube, the sample was discarded and the contralateral jugular vein used. Lactate was then measured in duplicate (NOVA Statprofile M; Nova Biomedical, Waltham, Massachusetts, USA) within 5 minutes of blood collection on Day (D) 0, D4 and D14 for all study groups. Data were analysed with a general linear

model for repeated measures and *post hoc* t tests with Bonferroni's correction. P values of < 0.05 were considered significant. Results are mean ± SD.

Results

Physical examinations, biochemistry profiles and complete blood counts were within reference limits for all dogs. All dogs drank and ate well throughout the entire study. Compared to the control group, LOW and HIGH groups had significantly higher blood lactate levels at D4 ($p < 0.0001$ and $p < 0.0001$ respectively) and D14 ($p=0.007$and $p=0.0001$ respectively). There was no difference between treatment groups at D0 (LOW, $p=0.65$ and HIGH, $p=0.14$; see Table). There was no effect of time within the control group ($p>0.29$). Within the LOW and HIGH groups, blood lactate was increased at D4 ($p<0.0001$) and D14 ($p=0.003$ and $p = 0.0001$ respectively) versus D0 (see Table). In the LOW group, blood lactate was greater at D4 than D14 ($p=0.02$). Blood lactate was greater in the HIGH group than the LOW group at D14 only ($p=0.001$).

Discussion

Healthy dogs treated with antiinflammatory and immunosuppressive doses of prednisone (1.0 to 4.0 mg/kg po SID) have statistically and clinically significant increases in blood lactate levels within 4 days of starting therapy. These changes can be considered clinically significant as they exceed the normal range of blood lactate in healthy dogs ($< 2.x$ $mmolL^{-1}$; Pang) and may therefore alter the course of therapy. As none of the dogs in this study showed signs of hypoperfusion based on daily complete physical examinations, it is most likely that the glucocorticoid dogs developed a type B hyperlactatemia (not associated with hypoperfusion). The effects

of lower doses of glucocorticoids, the time to onset of hyperlactatemia and the long term effects of glucocorticoids on blood lactate levels in dogs requires further study. Steroids have known effects on carbohydrate metabolism (Henneman, McMahon) and it has been demonstrated that people with Cushing's syndrome or those receiving 17-hydroxycorticosteroids, have significantly elevated blood concentrations of lactate and pyruvate (Henneman). In addition, those patients found to have elevated lactate levels in association with Cushing's syndrome had values return to normal following subtotal adrenalectomy (Henneman).

It has been suggested that increased lactate levels following glucocorticoid administration are due to a marked increase in gluconeogenesis from protein (Forbath). This increased gluconeogenesis is subsequently associated with an increased rate of glucose production and utilization. The enhanced utilization of glucose in turn is believed to account for an increased formation of lactate and an increased concentration of lactate in the blood (Forbath). It has been hypothesized that the specific site of action of glucocorticoids involves the hormonal inhibition of the conversion of pyruvic acid to Acetyl CoA, which results in decreased pyruvic acid oxidation and the subsequent accumulation of lactic and pyruvic acid (as lactic acid appears to be largely oxidized rather than repolymerized to glycogen). Additionally, it is believed that glucoroticoids enhance amino acid utilization and their conversion to pyruvate. Lactate concentrations would be expected to increase as pyruvate concentration increases (Henneman).

In conclusion, the administration of prednisone to dogs at antiinflammatory and immunosuppressive doses (1 to 4 mg/ po BID) results in a clinically significant hyperlactatemia. This hyperlactatemia is most likely type B in origin. Given that therapy for type A and type B hyperlactatemia vary greatly, it is important to carefully interpret hyperlactatemia in patients that may be hypoperfused and concurrently

receiving glucocorticoids, as the elevation in lactate may be the result of type A or type B hyperlactatemia, or a combination of the two.

Approval for this study was granted by the Ethics Committee (CEUA) of the Université de Montréal.

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Table: mean +/- SD for blood lactate ($mmolL^{-1}$) in healthy dogs receiving placebo (CONTROL), LOW ($1\ mgkg^{-1}$) or HIGH ($4\ mgkg^{-1}$) doses of oral prednisone once daily for 14 days. Identical letters within columns denote significant differences. Identical numbers within rows denote significant differences. A p value < 0.05 was considered significant.

Treatment	Day 0	Day 4	Day 14
CONTROL	0.5 ± 0.3	$0.4 \pm 0.4^{a,b}$	$0.9 \pm 0.5^{c,d}$
LOW	0.7 ± 0.2^{1}	$3.4 \pm 0.9^{a,1}$	$2.3 \pm 1.5^{c,e,1}$
HIGH	$1.0 \pm 0.6^{2,3}$	$3.1 \pm 0.7^{b,2}$	$4.3 \pm 0.7^{d,e,3}$